

AD 756585

Report Number 7

ORGANOTINS FOR ANTIMALARIAL SCREENING

Final Report

by Henry G. Kuivila

5 January 1973

Supported by

U. S. Army Medical Research and Development Command

Washington, D. C. 20315

Contract DA-49-193-MD-3018

Research Foundation of the State University of New York

Albany, New York 12224

This document has been approved for public release

and sale; its distribution is unlimited.

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

DISCLAIMER NOTICE

**THIS DOCUMENT IS BEST QUALITY
PRACTICABLE. THE COPY FURNISHED
TO DTIC CONTAINED A SIGNIFICANT
NUMBER OF PAGES WHICH DO NOT
REPRODUCE LEGIBLY.**

TABLE OF CONTENTS

I.	General Summary
II.	Synthetic results.....
A.	Sulfones.....
B.	Allenyltins.....
C.	Bi- and Tricyclic Organotins.....
D.	Nitrogen-containing Organotins.....
E.	Organotin-Schiff Base Complexes.....
III.	Experimental.....
A.	Allyltin Compounds.....
B.	Sulfones.....
C.	Allenyltins.....
D.	Bi- and Tricyclic Organotins.....
E.	Nitrogen-containing Organotins

LIST OF TABLES

Table II The Physical Properties and Analyses of Allylalkyltin Compounds	27
Table III THE UV SPECTRAL DATA OF ALLYLTIN COMPOUNDS . .	28
Table IV The Physical Properties and Analyses of Sulfones	31
Table V Allenyl and Propargyltins	35
Table VI ANALYTICAL DATA ON PYRIDYL TINS	46

ORGANOTINS FOR ANTIMALARIAL SCREENING

Summary of Final Report

When new strains of malaria were discovered in Southeast Asia which did not respond to treatment by the usual antimalarials quinine and chloroquine, an extensive screening program for new antimalarials was initiated at the Walter Reed Army Institute of Research. It was discovered that certain organotins displayed activity toward some of these parasites. The author of this report was invited to submit a proposal for the synthesis of compounds which might show promise. A long range proposal was submitted and formed the basis of the research conducted under this contract.

It was proposed to prepare for screening organotins in four general categories: 1) preparation of a variety of relatively simple organotins for general screening; 2) introduction of organotin groups into quinine and its derivatives; 3) introduction of organotin groups into 4-aminoquinoline; 4) introduction of organotin groups into sulfones which had shown some antimalarial activity.

During the course of the contract it was possible to carry on research on three of these categories. However, successful synthetic results were obtained only in the first of these. A total of forty three compounds was submitted for testing, and test results were returned of thirty six of these. These included: sulfones, alkylallyltins; alkylallenyltins; alkylpyridyltins; and bis-salicylidenediaminoethane-alkyltin halide complexes. Some showed activity in mice, but were inactive or toxic in birds; and vice versa. None was active in both, and many were toxic in one or both.

ORGANOTINS FOR ANTIMALARIAL SCREENING

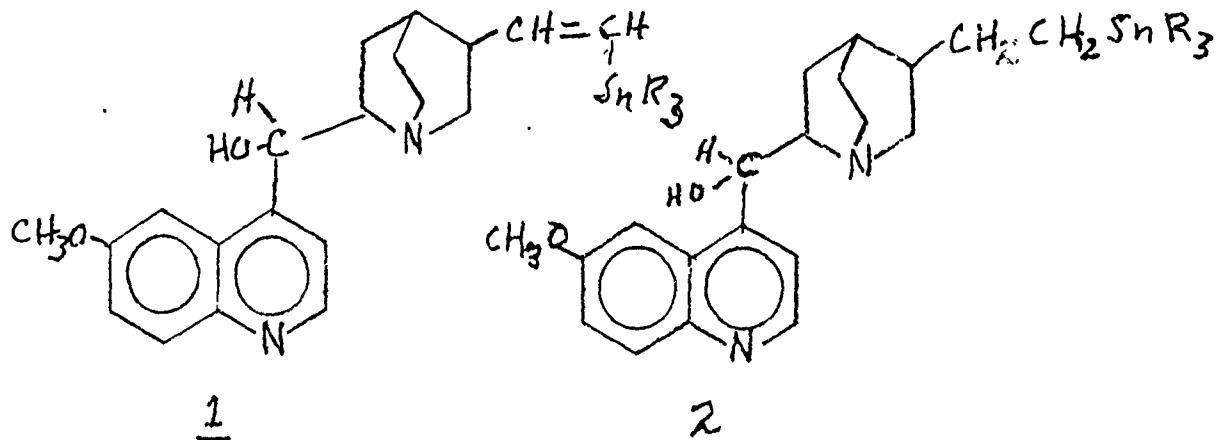
I. General Summary

When new strains of malaria were discovered in Southeast Asia which did not respond to treatment by the usual antimalarials, quinine and chloroquine, an extensive screening program for new antimalarials was initiated at the Walter Reed Army Institute of Research. It was discovered that certain simple organotins displayed activity toward some of these parasites. The author of this report was invited to submit a proposal for the synthesis of compounds suitable for antimalarial screening. A long range proposal was submitted and formed the basis of the research conducted under this contract. During the two years of the contract it was possible to complete only a portion of the longer range goals.

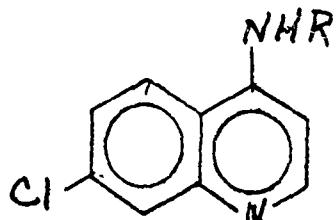
It was proposed to carry on research under two broad categories:

- 1) modification of known antimalarials by the introduction of organotin functions; 2) preparation of a variety of simple organotins in the hope that some would be found to be active.

In the first category one of the more promising objectives involved the modification of quinine to form compounds of structures 1 and 2. Apparently simple routes for their preparation are available, but no success was realized.



It was also hoped to modify the aminoquinoline group of antimalarials by introduction of an organotin group to form compounds such as 3. However, time did not permit experimentation in this direction. The third class, whose synthesis was attempted unsuccessfully, were crotyl sulfones containing



organotin functions: $(R_3SnCH=CHCH_2)_2SO_2$ and $CH_3CH(SnR_3)CH=CHSO_2CH_2CH=CHCH_3$.

However, forty three more simple compounds were prepared and submitted for screening. These are listed in Table I. The table includes all of the screening results made available to us. It will be noted that a number of the compounds are toxic to mice or chicks, or both. However, a few (7-9,11) are active in mice and, in the cases of 8 and 9 are inactive in chicks. In summary, it may be said that none of the compounds tested showed any real promise as antimalarials.

ORGANOTINS SUBMITTED FOR ANTIMALARIAL SCREENING

Submitter code 0378

		screening results ^a		
		M ^b	B ^c	P ^d
1.	phenyl propargyl sulfone, WR-49464-B	t		
2.	phenyl crotyl sulfone, WR-84820-A	i		i
3.	phenyl allyl sulfone, WR-84818-A	i		i
4.	ethyl propargyl sulfone, WR-84819-A	i		i
5.	tetrallyltin, WR-73750-B	i		
6.	allyltrimethyldtin, WR-80280-A	t		
7.	triethylallyltin, WR-80281-A	a		
8.	allyltri-n-propyltin, WR-80282-A	a	i	
9.	allyltri-n-butyltin, WR-80283-A	a	i	
10.	diallyldimethyldtin, WR-80284-A	i		
11.	diallyldi-n-propyltin, WR-80285-A	a		
12.	diallyldi-n-butyldtin, WR-80286-A	i		
13.	diallyldiethyltin, WR-80287-A			
14.	triallylmethyldtin, WR-92109-A			
15.	triallylethyltin, WR-92089-A			
16.	triallyl-n-propyltin, WR-92090-A		i	
17.	triallyl-n-butyltin, WR-92091-A			
18.	triallylphenyltin, WR-92092-A			
19.	diallyldiphenyltin, WR-59215-C		i	
20.	allyltrichenyldtin, WR-27343-C			
21.	tri-n-butylallenyltin, WR-27343-C	t	i	
22.	triphenylallenyltin, AF58635		i	ao, cs
23.	tripropylallenyltin, AF58662	t	t	
24.	triphenylallenyltin, AF58671	t	t	
25.	di-n-butylidiallenyltin, AF58680	t	i	

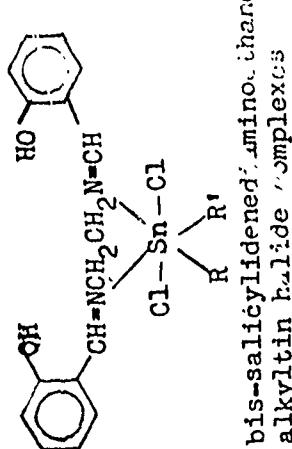
Table I (contd)

	M ^a	B ^b	P ^c
26. di-n-propylallenyltin, AF58706	i	t	
27. p-tri-n-butylstannyl-N,N-dimethyl-aniline, AF58699	t	i	
28. 2-trimethylstannyl-5(or 6)-trichloromethyl-6(or 5)-chlorobicyclo/2.2.1/heptane, AF58617	t		
29. 2-trimethylstannyl-5(or 6)-thiophenylbicyclo/2.2.1/heptane, AF58626	t		
30. 2(or 3)-trimethylstannyl-5(or 6)-tri-n-butylstannylbicyclo/2.2.1/heptane, AE72425	i	i	
31. bis-2(or 3),5(or 6)-trimethylstannylbicyclo/2.2.1/heptane, AE72416	t	a	
32. 3-trimethylstannyltricyclo/2.2.1.0 ²⁻⁶ /heptane, **			
33. penta-2,3-dien-2-yltrimethyltin, AE72443	t	i	
34. penta-2,3-dien-2-yltri-n-butyltin, AE72434	a	t	
35. tri-n-propyl-3-pyridyltin, **	t		
36. tri-n-butyl-3-pyridyltin, **	t		
37. n-butyl-tris-(3-pyridyl)-tin, **			
38. triphenyloroparazyltin, **	t	i	ps
40. R, R' = CH ₃ , AC94921	t	i	
41. R, R' = C ₂ H ₅ , AC94930	t	i	
42. R, R' = n-C ₃ H ₇ , AC94949	t	i	
43. R = CH ₃ ; R' = Cl, AC94958	i	i	

Key: a, active; i, inactive; t, toxic; ao, abnormal oocytes; cs, complete suppression; ps, partial suppression.

^a Mice; ^b White leghorn chicks; ^c Plasmodium gallinaceum infected Aedes aegypti

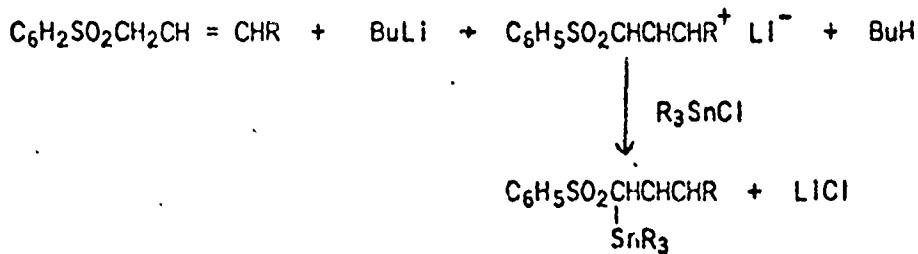
** No accession number available.



SYNTHETIC RESULTS

A. Sulfones. - Sulfones with α -hydrogen have been routinely converted to monoanions by a variety of basic reagents including methyl magnesium bromide,¹ n-butyllithium,² potassium t-butoxide,³ sodium hydride,⁴ and lithium amide.⁵

Field and McMurry⁶ indicated that n-butyllithium was the most effective metalation reagent, and benzene as solvent afforded better yields than ether or tetrahydrofuran. We have attempted to prepare organotin substituted sulfones by the following reaction sequence.



However, the products sought did not form, presumably due to the low nucleophilicity of the sulfonylallyl anion, and the relative weakness of the tin-carbon bond adjacent to the sulfonyl group.

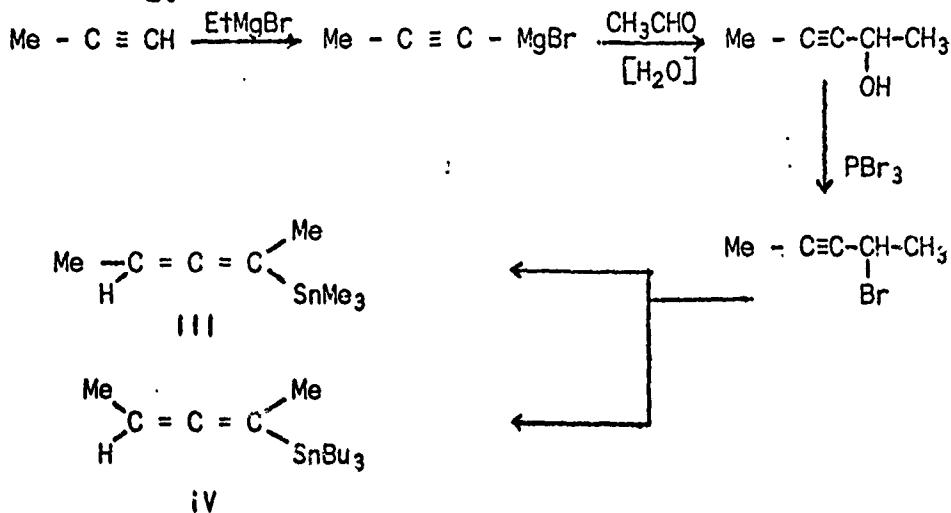
An alternate attempt to prepare organotin substituted sulfones involved the addition of triethyltin hydride to phenyl propargyl sulfone. Whereas simple acetylenes undergo facile addition of organotin hydrides, the sulfone was impervious to triethyltin hydride.

B. Allenyltins. - The groups bonded to the terminal carbon atoms in alenes exist in two planes perpendicular to each other. The allene molecule is, therefore, dissymmetric if the groups present on either of the terminal carbon atoms are not the same.

One of the main areas of interest in allene chemistry is the syntheses and resolution of optically active compounds. Recently, the resolution and absolute configuration of 1,3-dimethylallene has been carried out by Waters and Caserio.⁶

With a view to study the stereochemistry of allenyltin

derivatives, compounds III and IV have been prepared by the method described earlier.¹

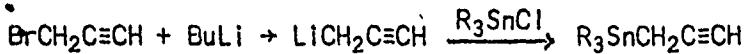


Amalgamated magnesium, prepared by stirring magnesium turnings in an etherial solution of mercuric chloride, was used for preparing the Grignard reagent from 2-bromo-3-pentyne. Still, the yield of allenyltin compounds was considerably low (~25-30%), probably due to coupling reactions. The use of cyclic Grignard reactor did not prove of any advantage.

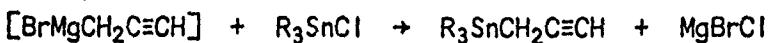
The allenyltin derivatives prepared by the above method were contaminated with substantial amounts of unreacted trialkyltin chloride. However, they could be easily purified by treating aqueous KF and removing white precipitate of trialkyltin fluoride. After careful fractionation, the allenyltins were obtained in ~90% purity.

The Propargyl/Allenyltin System. - This system was studied because of the structural similarity of the compounds to the allyltins prepared and submitted earlier by Mr. Kawakami; it has not previously been studied in any great detail, though Le Quan and Cadot^{8,9} have published some results on it, while Cochran and Kuivila¹⁰ have studied substituted allenyltins.

Two methods were used to prepare these compounds. Firstly, propargyl bromide was treated with n-butyllithium (hopefully to give the propargyllithium), and the product reacted with the appropriate trialkyltin halide.



The second method used was that described in the literature, namely treatment of the Grignard reagent derived from propargyl bromide with the appropriate trialkyltin halide.



In all cases studied ($\text{R}=\text{Et}, \text{Bu}, \text{Ph}$) the products obtained from the reaction scheme shown in eq. I were neither allenyl nor propargyltins, but propynyltins $\text{R}_3\text{SnC}\equiv\text{C}-\text{CH}_3$, as evidenced by I.R. and P.M.R. spectroscopy. This is probably due to rearrangement of the lithium derivative: it was found that on adding propargyl bromide to butyllithium in ether at low temperatures, a yellow color first built up in the solution, but within a few seconds disappeared. This behavior was observed at various temperatures and at various rates of addition of propargyl bromide and, also, if the butyllithium was added to the propargyl bromide.

The results obtained when the Grignard route was used were rather more complex. Gaudemar and co-workers have suggested that the Grignard reagent derived from propargyl bromide is entirely allenic,^{9,10} this conclusion is not borne out by the work reported here.

Allenyltins are characterized by a band in the infrared at ca. 1930 cm^{-1} ($\text{C}=\text{C}=\text{C}$), while propargyltins have a band at ca. 2110 cm^{-1} ($\text{C}\equiv\text{C}$) and propynyltins a band at ca. 2160 cm^{-1} ($\text{C}\equiv\text{C}$).

The product obtained when the Grignard prepared from propargyl

bromide and magnesium in ether was treated with Bu_3SnCl was a mixture of tributylpropargyl- and tributylallenyl-tin, and on standing for about a day, the propargyl compound isomerized to the allenyl compound. When the preparation was repeated using magnesium amalgam rather than magnesium metal, no trace of the propargyl isomer was observed in the product.

Similarly, triethyltin chloride and the Grignard (magnesium amalgam) gave only the allenyl isomer, but this (though in an impure state) isomerized on standing to the propynyl isomer ($Et_3SnC\ C-CH_3$).

A more exhaustive series of investigations was carried out in the case of triphenyltin chloride; here, it had been reported that the propargyl and allenyl isomers could be isolated and were both stable. (This is the normal trend in organotins, aryltin compounds generally being more stable than alkyltins.) Here the Grignard was prepared in three different ways:-

- a) Propargyl bromide/Mg amalgam/ether

Here the product mixture contained triphenylallenyltin and triphenylpropargyltin in the ratio 2:1, with a trace of the propynyl derivative.

- b) Propargyl bromide/Mg metal/ether.

The product mixture contained the allenyl and propargyl isomers in the ratio 1:6, and the propargyl isomer was obtained in a pure state, the physical properties agreeing with those quoted by Le Quan and Cadot.

- c) Propargyl bromide/Mg metal/THG

The product mixture contained no propargyltin, but included allenyl and propynyltins.

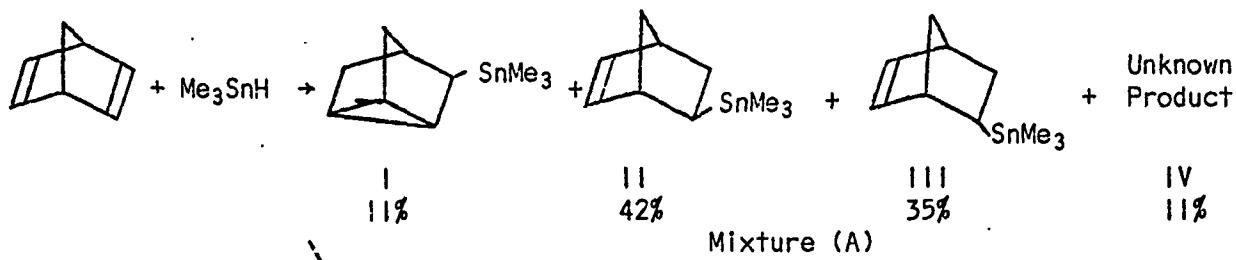
Thus, it appears that this particular system is extremely labile, and that under only slightly differing conditions various product mixtures may be obtained. The isolated triphenylpropargyltin will be submitted but, at the present time, we do not plan to carry out any further studies on this particular system.

C. Bi- and Tricyclic Organotins. - Although ionic additions to norbornadiene has been studied extensively,¹¹ the analogous free radical additions have received comparatively little attention. p-Theocresol has been shown to add to norbornadiene, giving a mixture of exo-5-norbornen-2-yl p-tolyl sulphide and 3-nortricyclyl-p-tolyl sulphide.¹² p-Tolyl sulphonyl chloride,¹³ perfluoropropyl iodide¹⁴ and bromotrichloromethane,¹⁴ however, gave the corresponding 3,5-disubstituted nortricyclo[4.2.1]octanes. Carbon tetrachloride, chloroform and diethylphosphite, on the other hand, gave the corresponding 3-nortricyclyl derivative as the major product.¹⁵

The present investigation was undertaken as a part of the extensive study of free radical additions of organotin hydrides to unsaturated compounds being carried out in these laboratories in order to provide more organotins for screening.

Trimethyltin hydride reacted readily with norbornadiene on photolysis; an equimolar mixture in a pyrex sealed ampoule to give a

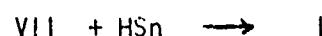
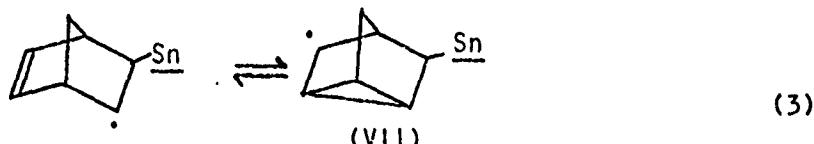
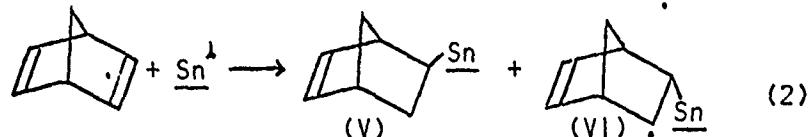
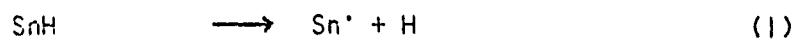
mixture (A), b.p. 35°/0.02 mm., containing four components.



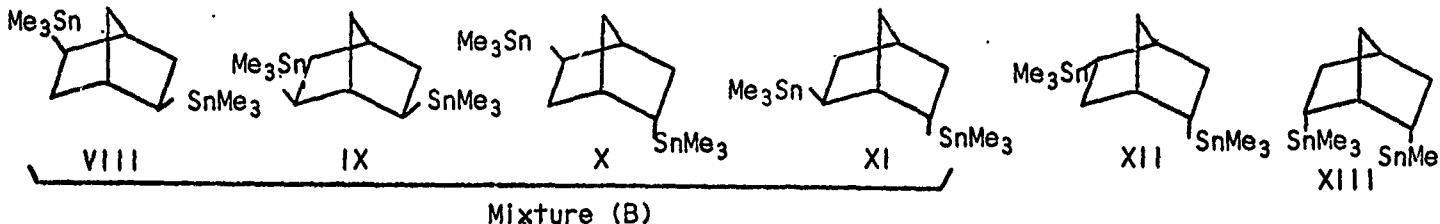
The ratio of the components was as shown above. The same mixture was obtained when the reaction was carried out thermally or photolytically in a quartz tube.

On a 1,2,3-tris- β -cyanoethoxypropane (TCEP) column, compounds I and II show the same retention times whereas on an Apiezon column, compounds II and III show same retention time. Compound I was identified by independent synthesis from 3-bromonortricyclene¹⁶ and trimethyltin chloride via the Grignard method. Compounds II and III have previously been characterized by Francis Pelczar in these laboratories.¹⁷

The free radical chain nature of such additions has been well substantiated and the following equations account for the formation of Compounds I - III ($\underline{\text{Sn}} = \text{Sn}^{\cdot}\text{e}_3$).

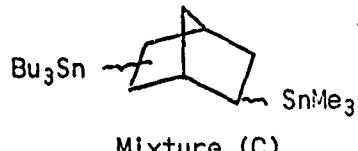


When mixture (A) (b.p. $35^\circ/0.02$ mm) was photolysed with excess trimethyltin hydride (~ 2 moles), Compounds I and IV remained unchanged but II and III reacted further and gave a mixture (B) of diadducts (b.p. $82^\circ/0.02$ mm). Mixture (B) shows only three peaks on SE30 column and four peaks on apiezon column. This mixture possibly contains Compounds VIII - XI. The formation of compounds XII and XIII is most unlikely on steric grounds.



The interaction of mixture (A) with trimethyltin hydride was carried out under various conditions, photolytically as well as thermally and in every case mixture (B) was obtained. Similar results were observed when the reactions were carried out between norbornadiene and excess (~ 2.5 moles) trimethyltin hydride.

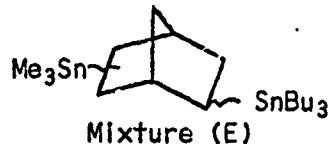
Addition of tributyltin hydride to mixture (A) was comparatively slower. However, in this case also, compounds I and IV remained unchanged but II and III gave a mixture (C) of bisadducts quantitatively (b.p. $135^\circ/0.02$ mm).



Tributyltin hydride reacted with norbornadiene in equimolar ratio to give a mixture (D) of monoadducts (b.p. $105^\circ/0.02$ mm). This mixture possibly contains the exo and endo norbornyl as well as the nortricyclyl derivatives. No attempt was made to isolate the different

components or to determine their relative ratio in the mixture. On S.E.30 column, the mixture shows only two not well separated peaks; the small peak may be due to nortricyclic compound and the big peak due to exo and endo isomers.

Mixture (D) reacted with excess trimethyltin hydride very slowly to give a mixture (E) of diadducts, (b.p. 135°/0.02 mm).



Mixtures (C) and (E) seem to consist of the same isomers. They have identical boiling points and their infra-red spectra are virtually identical. However, the relative ratio of the isomers is not the same in the two mixtures as shown by g.l.p.c. on S.E. 30 column.

As expected, the attack of trifluoroacetic acid on mixture (B) was found to be extremely slow. On stirring the mixture with excess trifluoroacetic acid (~ 6 moles) in pentane for four days, a white solid gradually precipitated out with evolution of methane. The infra-red spectrum of the solid showed that all methyl groups were not cleaved.

D. Nitrogen-containing Organotins.

Simple Quinolines. - In the preparation of 2-triethyltin-4-methyl quinoline from 2-chloro-4-methyl quinoline with butyllithium in anhydrous ether, followed by the addition of triethyltin chloride, a compound, m.p. 57-58.5°, was obtained. The nmr spectrum indicated quinoline protons, methylprotons, and ethyl protons at τ 7.5, τ 2.5 and τ 1.0 with the relative integrated intensities in the ratio of 28:19:90 (5:3:15), respectively. However, the elemental analysis did not give a satisfactory result, indicating there was impurities present in the compound. Therefore, further purification is necessary before submitting for anti-malarial screening.

For the preparation of 3-trialkyltin quinoline, the final products were viscous liquids. Distillation or recrystallization failed to lead to the desired compound. It appears that the halogen-metal exchange reaction goes to completion as shown by the color test for lithium quinoline. In addition to the desired 3-trialkyltin quinoline, the coupling product, diquinoyl might be formed as side product which could contaminate the desired compounds.

B. 7-Chloroquinolines. - Attempts have been made to prepare 4-triethylstanny 7-chloroquinoline by three methods: a) treatment of the dichloro compound with n-butyl lithium at -40° to -50°, followed by treatment of the lithium derivative with tributyltin chloride, b) treatment of the dichlorocompound with tributyltin lithium, and c) preparation of 4-lithio 7-chloroquinoline from the dichlorocompound and lithium metal, followed by treatment with tributyltin chloride.

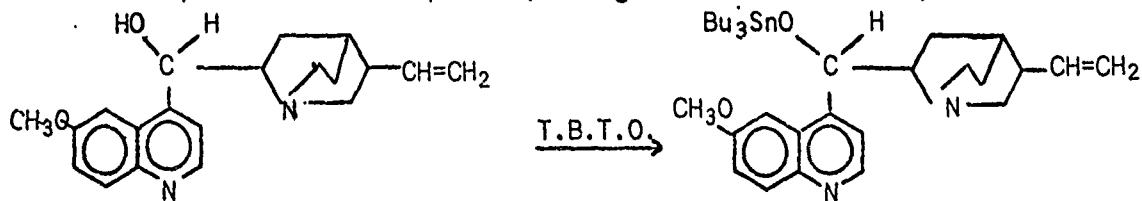
Neither method b) nor c) was successful. Method a) produced

a mixture of several components with no major component under the conditions first used (addition of butyl lithium at -45° to a THF suspension of 4,7-dichloroquinoline, followed by addition of tributyltin chloride at room temperature), but a change in conditions (diethyl ether as solvent, addition of tin halide at -40°, addition of excess ammonium chloride solution before workup) produced a mixture with two major components; distillation, followed by G.L.C. analysis, showed the more volatile of these to be unreacted tributyltin chloride. The other component could not be obtained in anything approaching a pure state.

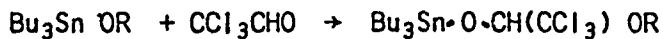
However, the recovery of tributyltin chloride in such a high yield (>60%) indicates that in this case the problem is complicated by coupling of two quinoline nuclei, involving some quinolyl lithium as an intermediate.

In the case of 2-chloroquinoline and of other quinoline derivatives studied by Dr. K. C. Yeh, where butyl lithium is added to a solution of the quinoline derivative rather than a suspension, the reaction appears to be quite straightforward.

C. Quinines. - It was found that quinine could be readily converted into its tin alkoxide by azeotropic dehydration of a mixture of bistributyltin oxide and quinine, using toluene as solvent,



but that the compound so formed, in common with other tin alkoxides, was too readily hydrolyzed by moisture in the air to be of any value. If did, however, react like simple alkoxides with acceptor molecules such as phenyl isocyanate and chloral:



The products of these reactions are also very readily hydrolysed; however, the hydrolysis products have been isolated and will be submitted when satisfactory analytical data have been obtained.

A second approach used was to attempt to convert the ethylenic group in both quinine and cinchonine to an acetylenic group by bromination and subsequent dehydrobromination and then to add trialkyltin hydrides to this group. However, we were unable to repeat earlier work reported in the literature⁴ which indicated that this had been done.

Attempts to replace the hydroxyl group of quinine by bromine, which could then perhaps be replaced by a trialkyltin group, were also not successful.

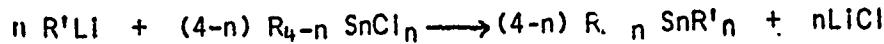
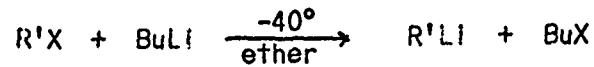
D. Alkylpyridines. - Gilman¹⁸ has reported the preparation of triphenyl-2- and -3-pyridyltin. His method has been used and extended to prepare the following compounds. The purity after distillation of the compounds, as calculated from G.L.C. traces, is given in parenthesis.

$\text{Bu}_3\text{Sn 2-py}$	(87%)	b.p. 103-105°/.075 mm
$\text{Bu}_3\text{Sn 3-py}$	(97%)	b.p. 106.5-108°/.075 mm
$\text{Bu}_2\text{Sn(2-py)}_2$	(95%)	b.p. 130-132°/.1 mm
$\text{Bu}_2\text{Sn(3-py)}_3$	(91%)	b.p. 154-158°/.075 mm
$\text{Pr}_3\text{Sn 2-py}$	(95%)	b.p. 96°/.15 mm
$\text{Pr}_3\text{Sn 3-py}$	(88%)	b.p. 91-93°/.1 mm

These compounds will be submitted when purification procedures (where necessary) have been carried out and when satisfactory analytical data become available.

The reaction scheme used in c) and d) may be summarized as

follows, where R is n-butyl or n-propyl R' may be pyridyl or quinolyl,
X is halido:



N-Tri-n-butylsulfanilamide. - This compound was prepared during the course of Dr. Mitchell's Ph.D. research. The preparation has been repeated as this compound is an organotin derivative of a known anti-bacterial and contains a relatively unreactive tin-nitrogen bond; the compound can be handled in air for short periods without any appreciable hydrolysis occurring.

E. Organotin Schiff Base Complexes. - So far, our efforts have involved the ligand, bis(salicylidenediaminoethane (BSDE•2H) and two other ligands were checked as possible chelating agents, but they turned out to be hopeless. The preparative procedure was a deprotonation reaction of BSDE•2H by means of Bu_2SnO , $Bu_2Sn(O\text{Me})_2$ and $Bu_2Sn(NEt_2)_2$. In all cases, reactions gave H_2O , CH_3OH and $NH(C_2H_5)_2$ but the products always had wide melting ranges. In one typical case (Bu_2SnO) the product was run through a column packed with neutral alumina and T.H.F. The solid product obtained after evaporation of T.H.F. was recrystallized several times from n-heptane, and yellow crystals with m.p. of 154-156°C were obtained. Starting from 8 g. of crude product, only 0.5 g. of crystals were recovered.

In order to check the coordination ability of nitrogen atoms in BSDE 2H molecule, reactions between organotin chlorides and the ligand were tried. Four simple addition compounds have thus been prepared: $R_2SnCl_2 \cdot BSDE \cdot 2H$ ($R = CH_3$, C_2H_5 and $n-C_3H_7$) and $C_2H_5SnCl_3 \cdot BSDE \cdot 2H$. A reaction between trimethyltin chloride and BSDE•2H was carried out but no immediate precipitation of adduct was observed. Thus, trialkyltin chloride does not have enough acceptor capacity toward this ligand which seems to function well as a bidentate ligand. No hexa-coordinated trialkyltin chloride adduct has been reported. All of these compounds showed good C, H, N, Cl, and Sn analyses. Therefore, if the Sn-O bond formation occurred, these nitrogen atoms would be able to coordinate to tin atom if the conformation were favorable.

Some features of n.m.r. spectra of the BSDE2H ligand, $(CH_3)_2SnCl_2 \cdot BSDE \cdot 2H$ and Bu_2SnO ($Bu_2Sn(BSDE)$) merit comment. There are

four typical protons: $-\text{CH}=\text{N}-$, aromatic ring, $=\text{N}-\text{CH}_2-$ and alkyl protons attached to tin in order from the low field to the high field. They are summarized in Table I.

TABLE I

τ VALUE (p.p.m.) OF BSDE2H AND ITS TIN COMPLEXES

Compound	$-\text{CH}=\text{N}-$	$=\text{N}-\text{CH}_2-$	$\text{Sn}-\text{CH}_3$	Solvent
BSDE2H	1.68	6.15	-	CH_2Cl_2
$(\text{CH}_3)_2\text{SnCl}_2 \cdot \text{BSDE2H}$	1.65	6.03	8.84	CDCl_3
$\text{Bu}_2\text{Sn}(\text{BSDE})$	1.67 (1) 2.00 (9)	6.10 (2) 6.17 (8)	-	CDCl_3
$\text{Bu}_2\text{Sn}(\text{BSDE})$	1.62 (4) 1.98 (5)	6.08 (4) 6.19 (5)	-	CH_2Cl_2

In all these compounds, good relative intensity ratios were obtained. An interesting thing is that $(\text{CH}_3)_2\text{SnCl}_2\text{BSDE} \cdot 2\text{H}$ adduct shows only one set of $-\text{CH}=\text{N}-$ and $=\text{N}-\text{CH}_2-$ protons but $\text{Bu}_2\text{Sn}(\text{BSDE})$ complex shows two sets of these protons whose intensity changes depending on a small change of the solvent. One assumption in the case of $\text{Bu}_2\text{Sn}(\text{BSDE})$ is that the intramolecular motion sometimes favors the coordination of both nitrogen atoms which must be easier at low temperature. We assume a chelate structure by two nitrogen atoms forming a six-coordinated tin atoms in the case of the adducts, since only one set of $-\text{CH}=\text{N}-$ and $=\text{N}-\text{CH}_2-$ protons were observed.

As shown in Table I, $=\text{N}-\text{CH}_2-$ protons of $(\text{CH}_3)_2\text{SnCl}_2\text{BSDE} \cdot 2\text{H}$ are shifted to downfield by 0.12 p.p.m. from those of the ligand BSDE2H. This might be because nitrogen atoms coordinate to tin. Among two sets of $=\text{N}-\text{CH}_2-$ protons in $\text{Bu}_2\text{Sn}(\text{BSDE})$, the low field ones might be

attached to the nitrogen coordinated to tin. Among two sets of -CH=N- protons, the low field one could be attributed to the one adjacent to the coordinated nitrogen, and the high field one could occur because of the breaking down of a strong hydrogen bond which exists in the ligand itself.

BIBLIOGRAPHY

1. L. Field and J. W. McFarland, *J. Amer. Chem. Soc.*, 75, 5582 (1953).
2. W. E. Truce and R. D. Buser, *ibid.*, 76, 3577 (1954).
3. H. D. Becker and G. A. Russell, *J. Org. Chem.*, 28, 1896 (1963).
4. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1345 (1965).
5. L. Field and J. W. McFarland, *ibid.*, 75, 5582 (1953).
6. W. L. Water and M. C. Caserio, personal communication.
7. J. C. Cochran, Ph. D. dissertation, University Of New Hampshire, 1966.
8. M. Le Quan and P. Cadot, *Comtes rendus*, 254, 133 (1962).
9. M. L. Quan and P. Cadot, *Bull. Soc. Chim. France*, 1965 (1), 45.
10. H. G. Kuivila and J. C. Cochran, *J. Am. Chem. Soc.*, 89, 7152 (1967).
11. P. von R. Schleyee, *ibid.*, 80, 1700 (1958).
12. S. J. Cristol, G. D. Brindell and J. A. Reeder, *ibid.*, 80, 635 (1958).
13. S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, 26, 2182 (1961).
14. N. Ol Brace, *ibid.*, 27, 3027 (1962).
15. D. J. Trecker and J. P. Henry, *J. Am. Chem. Soc.*, 85, 3204 (1963).
16. J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong, *ibid.*, 72, 3116 (1950).
17. F. Pelczar, Ph. D. Thesis, University of New Hampshire, 1968.
18. H. Gilman and T. N. Goreau, *J. Org. Chem.*, 17, 1470 (1952).

III. EXPERIMENTAL

A. Allyltin Compounds

Allyltri-n-propyltin

Into a dry 250 ml three-necked flask equipped with a sealed stirrer, a reflux condenser and a pressure-equalized dropping funnel were placed 7.3 g. (0.30 g. atoms) of dry magnesium turnings and 100 ml of anhydrous ether. The flask was cooled in an ice bath, a few drops of ethylene dibromide were added and a solution of 11.5 g. (0.15 mole) of allyl chloride in an equal volume of anhydrous ether was added dropwise over a period of 1 hour. After the addition was completed, the reaction mixture was stirred for 30 minutes. The Grignard reagent was transferred by means of nitrogen pressure into a 500 ml flask similarly equipped. The residue in the first flask was washed with 20-30 ml of dry ether and the wash liquid was added to the second flask. Then a solution of 28.3 gr (22.3 ml, 0.10 mole) of tri-n-propyltin chloride in 20 ml. of ether was added to the Grignard reagent in the course of 1 hour during which the reaction mixture warmed to room temperature. The reaction mixture was heated to reflux for 3 hours, was cooled and hydrolyzed with saturated aqueous ammonium chloride solution until it showed two clear layers. The organic layer was separated and the inorganic layer was washed with ether. The combined organic layer and ether washings were washed by dry ammonia to remove any organotin chlorides. The white precipitate which was thought to be n-propyltin ammonia adduct was filtered off and the filtrate was concentrated and distilled under reduced pressure to give 16.1 g. (59%) of allyltri-n-propyltin, b.p. 114-115/13 mm.

The other allyltin compounds were all prepared in similar ways. Yields varied from 30% to 70%. Generally speaking, allylmagnesium bromide gave a better yield than the chloride.

Allytrimethyltin

The Grignard reagent was prepared from 7.4 g. (0.35 g. atoms) of magnesium turnings and 11.5 g. (0.15 mole) of allyl chloride in 120 ml. of ether. A solution of 19.9 g. (0.10 mole) of trimethyltin chloride in 50 ml. of ether was added. Thus, 14.4 g. (70%) of allytrimethyltin, b.p. 123°⁰C, was obtained.

Allyltriethyltin

The Grignard reagent was prepared from 3.2 g. (0.13 g. atoms) of magnesium turnings and 8.8 g. (0.115 moles) of allyl chloride in 50 ml. of anhydrous ether. A solution of 24.5 g. (0.10 mole) of triethyltin chloride in 20 ml. of ether was added. After treatment similar to the preparation of Allyltri-n-propyltin, 9.2 g. (37%) of allyltriethyltin, b.p. 71°⁰C/10 mm was obtained.

Allyltri-n-butyltin

The Grignard reagent was prepared from 3.2 g. (0.13 g. atoms) of magnesium turnings and 8.8 g. (0.115 moles) of allyl chloride in 50 ml. of ether. A solution of 32.6 g. (0.10 moles) of tri-n-butyltin chloride in 20 ml. of ether was added. Thus, 11.9 g. (36%) of allyltri-n-butyltin, b.p. 73-76°⁰C/0.09 mm. was obtained.

Allyltriphenyltin (H. Gilman and J. Fisch, J. Org. Chem., 20, 763 (1955))

To 0.1 mole of allylmagnesium bromide in 190 ml of dry ether was added 27.0 g. (0.0700 mole) of dry powdered triphenyltin chloride by means of a rubber tube connecting a solid vessel of the flask. The addition required 30 minutes and a lively reaction ensured. After stirring for two hours, the reaction mixture was worked up in the usual manner. (See the procedure for diallyldiphenyltin.) After drying, the ether layer and removing the solvent, there remained a pale yellow oil. This was refluxed with 100 ml. of petroleum ether (b.p. 77-115°) and then refrigerated. Filtration of the ether and concentration of the mother liquor gave a total yield of 24.0 g. (87.5%), melting at 73-75°. The analytical sample was obtained from 95% ethanol as colorless prisms and melted at 73.5-74.5°.

Diallyldimethyltin

The Grignard reagent was prepared from 5.4 g. (0.22 moles) of magnesium turnings and 15.3 g. (0.20 moles) of allyl chloride in 100 ml. of ether. A solution of 20.0 g. (0.09 mole) of dimethyltin dichloride in 10 ml. of T.H.F. and 40 ml. of ether was added. Thus, 7.5 g. (36%) of diallyldimethyltin, b.p. 62-63°C/15 mm. was obtained.

Diallyldiethyltin

The Grignard reagent was prepared from 6.4 g. (0.26 g. atoms) of magnesium turnings and 17.6 g. (0.23 moles) of allyl chloride in

130 ml. of ether. A solution of 24.8 g. (0.10 moles) of diethyltin dichloride in 10 ml. of T.H.F. and 40 ml. of ether was added. Thus, 7.4 g. (28%) of diallyldiethyltin, b.p. 49-52°C/mm. was obtained.

Diallyldi-n-propyltin

The Grignard reagent was prepared from 14.6 g. (0.60 g. atoms) of magnesium turnings and 23.0 g. (0.30 moles) of allyl chloride in 230 ml. of ether. A solution of 27.6 g. (0.10 mole) of di-n-propyltin dichloride in 40 ml. of ether was added. Thus, 7.3 g. (25%) of diallyldi-n-propyltin, b.p. 46-48°C/mm. was obtained.

Diallyldi-n-butyltin

The Grignard reagent was prepared from 14.6 g. (0.60 g. atoms) of magnesium turnings and 23.0 g. (0.30 moles) of allyl chloride in 230 ml. of ether. A solution of 30.4 g. (0.10 mole) of di-n-butyltin dichloride in 50 ml. of ether was added. Thus, 16.4 g. (52% of diallyldi-n-butyltin, b.p. 70-72°C/0.1 mm. was obtained.

Diallyldiphenyltin (H. Gilman and J. Eisch, J. Org. Chem., 20, 763 (1955))

Allylmagnesium bromide was prepared in an 85% yield by the addition of 40.8 g. (0.336 mole) of allyl bromide in 190 ml. of dry ether to 48.9 g. (2.02 g. atoms) of magnesium turnings suspended in dry ether over the course of 2 hours. The reagent was analyzed by titration of an aliquot with standard acid. To 0.10 mole of the allylmagnesium bromide so prepared were added 17.2 g. (0.050 mole) of diphenyltin

dichloride in 50 ml. of dry ether over 50 minutes. The addition was accompanied by smooth reflux and the formation of a white, gelatinous precipitate. After 1.5 hours of stirring Color Test I was negative. The reaction mixture then was hydrolyzed by pouring into cold ammonium chloride solution. The separated ether layer was dried over sodium sulfate and the ether was removed. The residue was distilled under a vacuum and a colorless fraction taken at 173-174° (5.5 mm.), n_D^{20} 1.6025. This weighed 12.5 g. and was a 70.3% yield.

Triallylmethyltin

The Grignard reagent was prepared from 37.9 g. (1.56 g. atoms) of magnesium turnings and 82.3 g. (0.68 miles) of allyl bromide in 470 ml. of ether. A solution of 55.1 g. (0.15 mole) of methyltin tribromide in 20 ml. of THF. and 50 ml. of ether was added. Thus, 20.0 g. (52%) of triallylmethyltin, b.p. 100-101/23 mm. was obtained.

Triallylethyltin

The Grignard reagent was prepared from 26.3 g. (1.08 g. atoms) of magnesium turnings and 49.4 g. (0.45 moles) of allyl bromide in 330 ml of ether. A solution of 25.4 g. (0.10 mole) of ethyltin trichloride in 20 ml. of ether was added. Thus, 11.9 g (44%) of triallylethyltin, b.p. 60-61/0.6 mm. was obtained.

Triallyl-n-propyltin

The Grignard reagent was prepared from 53.4 g. (2.28 g. atoms)

of magnesium turnings and 72.7 g. (0.95 moles) of allyl chloride in 600 ml. of ether. A solution of 42.3 g. (0.16 moles) of *n*-propyltin trichloride in 50 ml. of ether was added. Thus, 29.5 g. (66%) of triallyl-*n*-propyltin, b.p. 51-52°C/0.2 mm. was obtained.

Triallyl-*n*-butyltin

The Grignard reagent was prepared from 21.9 g. (0.90 g. atoms) of magnesium, turnings and 54.5 g. (0.45 moles) of allyl bromide in 300 ml. of ether. A solution of 28.2 g. (0.10 moles) of *n*-butyltin trichloride in 30 ml. of ether was added. Thus, 19.7 g. (67%) of triallyl-*n*-butyltin, b.p. 60-61°C/0.16 mm. was obtained.

Triallylphenyltin

The Grignard reagent was prepared from 29.8 g. (1.22 g. atoms) of magnesium turnings and 61.7 g. (0.51 moles) of allyl bromide in 360 ml. of ether. A solution of 30.2 g. (0.10 moles) of phenyltin trichloride in 50 ml. of ether was added. Thus, 15.5 g. (49%) of triallylphenyltin, b.p. 80-82°C/0.07 mm. was obtained.

Tetraallyltin

The Grignard reagent was prepared from 73.0 g. (3.0 g. atoms) of magnesium turnings and 181.4 g. (1.5 moles) of allyl bromide in 1 liter of ether. A solution of 180.4 g. (0.5 mole) of diallyltin dibromide (K. Sisido and Y. Takeda, J. Org. Chem., 26, 2301 (1961) in 100 ml of ether was added. Thus, 115 g. (80%) of tetraallyltin, b.p. 66-68°C/0.04 mm. was obtained.

Table II
The Physical Properties and Analyses of Allylalkyltin Compounds

Compound	Yield %	b.p.	χ_{C} found calc'd	χ_{H} found calc'd	χ_{Sn} found calc'd
Allyl Sn	80	50-51/0.1	51.04	50.93	42.6 41.94
Allyl ₃ EtSn	44	60-61/0.6	48.52	48.75	7.37 7.44
Allyl ₃ PrSn		51-52/0.2	50.85	50.57	7.94 7.78
Allyl ₃ BuSn	67	60-61/0.16	51.55	52.22	7.75 8.09
Allyl ₃ PhSn	49	80-82/0.07	56.28	56.48	6.37 6.32
Allyl ₂ Me ₂ Sn	36	62-63/15	41.49	41.61	7.04 6.99
Allyl ₂ Et ₂ Sn	28		46.22	46.36	7.70 7.79
Allyl ₂ Pr ₂ Sn	25	46-48/0.1	50.50	50.22	8.56 8.43
Allyl ₂ Bu ₂ Sn ^b		70-72/0.1	53.58	53.37	9.09 8.96
Allyl ₃ e ₃ Sn		123	35.93	35.19	7.06 6.89
Allyl Et ₃ Sn	37	71/10	43.96	43.77	8.36 8.16
Allyl Pr ₃ Sn	59	114-115/13	50.11	49.87	9.26 9.07
Allyl Bu ₃ Sn	36	73-76/0.09	54.48	54.41	9.60 9.74

TABLE III

THE UV SPECTRAL DATA OF ALLYLtin COMPOUNDS

Compounds	n-C ₆ H ₁₄		CH ₃ CN	
	λ _{max} (mμ)	ε _{max} × 10 ⁻⁴	λ _{max} (mμ)	ε _{max} × 10 ⁻⁴
AlI ₄ Sn	217	3.16	220	3.14
AlI ₃ MeSn	211	2.49	217	2.50
Et	210	2.77	217	2.96
Pr	208	2.98	215	2.88
Bu	209	3.05	214	2.74
AlI ₂ Me ₂ Sn	208	1.99	212	1.83
Et	208	1.94	212	1.99
Pr	208	1.89	211	1.80
Bu	203	2.00	212	2.03
AlI ₃ Na ₃ Sn	<210	--	210	1.07
Et	<200	--	203	1.29
Pr	<200	--	204	1.12
Bu	<200	--	<200	

B. PREPARATION OF SULFONES

Phenyl Propargyl Sulfone

Following the procedure of Overberger, 44.5 g. (0.4 mole) of phenyl propargyl sulfide in 300 ml of glacial acetic acid was cooled to 0° and 120 ml of 30% hydrogen peroxide was added during one hour. The solution was then heated at 80-90° for several hours and allowed to stand overnight. The solid sulfone was removed by filtration and washed with alcohol and water. Recrystallization from absolute ethanol obtained 43 g. (60%) of phenyl propargyl sulfone, mp 89-89.5°.

Anal. Calcd. for $C_9H_8SO_2$: C, 59.99; H, 4.48

Found: C, 59.64; H, 4.71

Phenyl Crotyl Sulfone (A.C. Cope, D.C. Morrison and L. Field, J. Am. Chem. Soc., 72, 60 (1950))

Phenyl crotyl sulfone, bp 98° (0.05 mm), was prepared in 40% yield as described by the method of Cope. A mixture of 51 g. (0.3 mole) of phenyl crotyl sulfide in 200 ml of glacial acetic acid was cooled to 0° in ice-bath and 100 ml of 30% hydrogen peroxide was added during one hour. The solution was then heated at 70-80° for several hours, allowed to stand overnight, diluted with an equal volume of water and extracted with 200 ml of chloroform. The extract was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The residue was vacuum distilled and 23.5 g. (40%) of phenyl-crotyl sulfone was obtained.

Phenyl Allyl Sulfone (A.C. Cope, D.E. Morrison and L. Field, loc. cit.)

Phenyl allyl sulfone, bp 86-88° (0.95 mm) was prepared in 45% yield from phenyl allyl sulfide and 30% hydrogen peroxide in glacial acetic acid as described above for the preparation of phenyl crotyl sulfone.

Ethyl Propargyl Sulfone

Ethyl propargyl sulfone, bp 63-65° (0.05 mm) was prepared in 30-40% yield from ethyl propargyl sulfide and 30% hydrogen peroxide in glacial acetic acid as described above for the preparation of phenyl crotyl sulfone. Carbon hydrogen analysis are in progress.

Ethyl Crotyl Sulfone

Ethyl crotyl sulfone, bp 54° (0.9 mm) was prepared in 30-40% yield from ethyl crotyl sulfide and 30% hydrogen peroxide in glacial acetic acid as described above for the preparation of phenyl crotyl sulfone.

Table IV
The Physical Properties and Analyses of Sulphones

Attempted preparation of α -benzenesulfonyltriethyltin. - The method used for the metalation of sulphones with n-butyllithium in benzene has been described by Truce and Buser.⁷ In a 500-ml three-necked round bottomed flask, fitted with a condenser, a dropping funnel and a mechanical stirrer, was placed 6 g. (0.03 mole) of phenyl allyl sulfone and 100 ml of anhydrous benzene. n-Butyllithium in hexane (1.9 g., 0.03 mole) was added slowly to the mixture with cooling, while a stream of nitrogen was passed through the system. The mixture was then refluxed approximately three hours and allowed to stir at room temperature for one hour. Triethyltin chloride (7.2 g., 0.03 mole) was added to the mixture and again it was refluxed for 72 hours. Filtration followed by vacuum distillation, led to recovery of approximately 60% of triethyltin chloride and starting sulfone.

Attempted addition of triethyltin hydride to ethyl sulfone by photolysis. - A two-necked Pyrex tube was evacuated, heated, flushed with argon and cooled. Ethyl propargyl sulfone (4 g., 0.03 mole), 10 ml of anhydrous ether, and triethyltin hydride (7.2 g., 0.03 mole) were introduced under a stream of argon and stoppered. The Pyrex tube was then irradiated with 100 W medium pressure mercury lamp at 25-30° for 216 hours. After removal of diethyl ether, distillation yielded only unreacted starting materials.

Attempted addition of triethyltin hydride to ethyl propargyl sulfone by thermo-method (AIBN). - A 250 ml three-necked flask was fitted with a condenser, dropping funnel, and magnetic stirrer. It was

evacuated, heated and filled with argon. Ethyl propargyl sulfone (4 g., 0.03 mole), 50 ml of anhydrous benzene, and 7.2 g. (0.03 mole) of triethyltin chloride were introduced to the flask. The mixture was removed under reduced pressure. Distillation yielded unreacted triethyltin chloride and ethyl propargyl sulfone, which were characterized by I.R. spectra and g.l.p.c. retention times.

C. PREPARATION OF ALLENYLTINS

Preparation of Triethylallenyltin

In a 3-necked 500 ml. round-bottomed flask fitted with a stirrer, reflux condenser and dropping funnel were placed magnesium (2.4g., 0.1 mole) and dry ether (70 ml.). Propargyl bromide (11.9g., 0.1 mole) in ether (15 ml.) was added slowly with stirring; the reaction was initiated by iodine. After all the propargyl bromide had been added, the mixture was stirred for two hours, then cooled to -60°. Triethyltin chloride (14.5 g., 0.06 mole) was added, and the mixture stirred and allowed to warm to -15°. Saturated ammonium chloride solution was added slowly to hydrolyse the mixture, which was then allowed to warm to room temperature; the ether layer was separated and dried over magnesium sulphate, which was then filtered off. The ether was removed and the remaining pale yellow oil distilled, the major fraction coming over at 55-56°/1.5 mm.

The colorless distillate was shown by I.R. to contain allenyltin but no propargyltin and by G.L.C. to consist of only one component.

This procedure was used for the other allenyl and propargyltins.

Preparation of 3-Chloro-1-phenyl-1-butyne

A solution of 20.0g. (0.137 mole) of 1-phenyl-1-butyn-3-ol in 25 ml. anhydrous ether and a solution of 23.8g. (0.20 mole) of thionyl chloride in 25 ml. anhydrous ether were added simultaneously, dropwise, to 250 ml. of refluxing ether containing 20.7g. (0.15 mole) of potassium carbonate. After the addition, the reaction mixture was allowed to

TABLE V

Allenyl and Propargyltins

Compound or Mixture	% Yield	$\nu_{C\equiv C}$ or $\nu_{C=C=C} \text{ (cm}^{-1}\text{)}$	m.p. °C	b.p. °C/mm.
$\left\{ \begin{array}{l} \text{Me}_3\text{SnCH=C=CH}_2 \\ \text{Me}_3\text{SnC}\equiv\text{C-CH}_3 \end{array} \right\}$	12	2110 s 2165 m		133-136
$\text{Et}_3\text{SnCH=C=CH}_2$	54	1928 s		55-56/1.5
$\text{Pr}_3\text{SnCH=C=CH}_2$	46	1928 s		86-88/1.5
$\text{Bu}_3\text{SnCH=C=CH}_2$	75	1928 s		112/1.25
$\text{Ph}_3\text{SnCH=C=CH}_2$	95	1928 s	61-62	
$\text{Ph}_3\text{SnCH}_2-\text{C}\equiv\text{CH}$	90	2110 w	81.5-83.5	
$\left\{ \begin{array}{l} \text{Bu}_2\text{Sn}(\text{CH=C=CH}_2)_2 \\ \text{Bu}_2\text{Sn}(\text{CH}_2\text{C}\equiv\text{CH}) \\ \text{Bu}_2\text{Sn}(\text{C}\equiv\text{CCH}_3)_2 \end{array} \right\}$	62	1928 s 2105 m 2163 m		100/1.5
$\text{Ph}_3\text{Sn(Me)C=C=CHMe}$	25		47-48	
$\text{Me}_3\text{Sn(Ph)C=C=CHMe}$	40			101-103/0.25

reflux for two hours, filtered and the filtrate washed with 50 ml. of water, five 50 ml. portions of 5% aq. sodium bicarbonate solution and finally with 50 ml. of water. The ether solution was dried over magnesium sulfate and distilled to give 3-chloro-1-phenyl-1-butyne (13.1g., 58%) at 75-77°/0.25 mm. (authentic infrared spectrum).

Preparation of 2-Bromo-3-pentyne

A mixture of 3-pentyn-2-ol (100 g., 1.19 moles), dry pyridine (20 ml) and dry ether (500 ml) was placed in a flask equipped with a dropping funnel, stirrer and a reflux condenser with a CaCl_2 guard tube. Phosphorus tribromide (150 g., 0.56 mole) was added dropwise to above with stirring and cooling (0°). After an initial period of five minutes, the cooling bath was removed and the ether was allowed to reflux while the rest of the phosphorus tribromide was added (30 minutes). The mixture was then heated at 55° with stirring for three hours, after which it was cooled (0°) and ice was slowly added to hydrolyze excess phosphorus tribromide. The ether layer was washed with saturated NaHCO_3 solution and saturated NaCl solution, dried over MgSO_4 and then distilled. The bromide (119 g., 68%) was obtained at 41-44°/20 mm.

Preparation of Penta-2,3-dien-2-yltrimethyltin

2-Bromo-3-pentyne (14.7 g., 1 mole) in dry ether (100 ml) was added very slowly (ten hours) to activated magnesium turnings (3.0 g.) in refluxing ether (50 ml). The resulting Grignard compound was slightly dark in color. Trimethyltin chloride (19.8 g., 1 mole) in ether (40 ml) was then added to it and the mixture was refluxed for two hours. It was hydrolyzed by saturated ammonium chloride (just enough to precipitate the magnesium salts as a solid crust) and the etherial layer was treated

with aqueous potassium fluoride solution. The white precipitate obtained was filtered off, and the ether layer was dried over MgSO₄. Distillation afforded the allenyltin compound (5.8 g., 25%) as a colorless liquid, b.p. 46-47°/15 mm.

Preparation of Penta-2,3-dien-2-yl tributyltin

This compound (10.7 g., 30%) was obtained as a colorless liquid, b.p. 85°/0.02 mm, by the same procedure as described in the previous experiment.

Preparation of Penta-2,3-dien-2-yltriphenyltin

Triphenyltin chloride (37.2g., 1 mole) in ether (50 ml.) was added to the Grignard reagent, obtained from 2-bromo-3-pentyne (14.7g., 1 mole) and magnesium (2.5 g.). The mixture was refluxed for two hours and hydrolysed by saturated ammonium chloride solution. The crude product obtained from the etherial layer was crystallized from methanol; m.p. 47-48° (yield 25%).

Preparation of 1-Phenyl-1,2-dien-1-yltrimethyltin

This was obtained as a colorless liquid, b.p. 101-103°/0.25 mm. in 40% yield from 3-chloro-1-phenyl-1-butyne and trimethyltin chloride by the same method as in the previous experiment.

D. PREPARATION OF BI- AND TRI-CYCLIC ORGANOTINS

General----- Trimethyltin

hydride and tributyltin hydride were prepared as reported earlier⁶. 3-Bromonortricyclene was obtained from norbornylene and N-bromosuccinimide as described in the literature⁷. Norbornadiene was distilled before use.

Photolysis was carried out in sealed pyrex or quartz ampules. A 100 w. mercury lamp was used as the light source. All experiments were carried out in argon atmosphere.

Interaction between Norbornadiene and Trimethyltin Hydride.

A. Equimolar Ratio. - A mixture of trimethyltin hydride (3.2 g.) and norbornadiene (1.8 g.) was sealed in a pyrex ampoule and was photolyzed for six hours at 55°. The ampoule was broken and the product was distilled to give a colorless liquid (mixture A) at 35°/0.02 mm. (4.5 g., 90%). The infrared spectrum was identical to that obtained by Mr. Pelczar.

- (1) The above experiment was repeated in a quartz tube. The photolysis was carried out for 27-1/2 hours. Identical results were obtained. The mixtures obtained in both

experiments showed the same ratio of components by g.l.p.c. on T.C.E.P. column.

(2) The mixture A (3.8 g.) from the above experiment was sealed in a quartz tube and photolyzed for eight days at 70°. The tube was broken and the mixture redistilled.

Infrared spectrum and g.l.p.c. showed that the mixture remained unchanged.

B. With excess Trimethyltin Hydride.

(1) A mixture of norbornadiene (1.36 g.) and trimethyltin hydride (6.5 g.) was heated under reflux (bath temp. 90°) with stirring for 17 hours. Excess trimethyltin hydride was removed at 20 mm. The product on distillation gave a small forerun (0.22 g., 5.8%) at 32°/0.02 mm and, finally, the main fraction (4.0 g., 65%) at 92°/0.02 mm, leaving a small residue.

Anal. Calc. for C₁₃H₄₀Sn₂: C, 37.02; H, 6.64. Found: C, 37.10; H, 6.60.

(2) A mixture of norbornadiene (1.8 g.) and trimethyltin hydride (8.0 g.) was sealed in a pyrex ampoule and photolyzed for 30 hours at 55°. Excess trimethyltin hydride was removed at 20 mm. Distillation afforded a small fraction (0.8 g.) at 35°/0.02 mm. Mixture B (6.8 g.) was finally obtained at 82°/0.02 mm.

(3) Similar results were obtained when the above experiment was repeated in a quartz tube.

Interaction between Mixture A and Trimethyltin Hydride.

(1) Trimethyltin hydride (3.5 g; 1.48 mole) was added

mixture A (3.66 g; 1 mole) in a pyrex ampoule which was sealed in argon atmosphere and photolyzed for 30 hours at 65°. After removing excess trimethyltin hydride and distilling the product, a forerun (0.4 g.) was obtained at 35°/0.02 mm and then mixture B (3.90 g.) distilled at 82°/0.02 mm.

(2) The above experiment was repeated twice, the photolysis being carried out for ten hours and two hours, respectively. Exactly similar results were obtained.

(3) Trimethyltin hydride (1.26 g., 0.5 mole) and mixture A (3.74 g.) were mixed in a pyrex ampoule and photolyzed for two hours at 65°. After the usual workup, the product was distilled to give first fraction (0.52 g.) at 35°/0.02 mm and the second fraction (3.06 g.) at 82°/0.02 mm. leaving a small residue. First fraction was unreacted mixture A with high ratio of Compounds I and IV.

Interaction between Mixture A and Tributyltin Hydride. - Tributyltin hydride (5.7 g., 1 mole) was added to mixture A (5.0 g.) in a pyrex tube which was sealed and photolyzed for six hours at 65°. Distillation of the product gave a first fraction (0.32 g.; b.p. 35-45°/0.05 mm.), a second fraction (2.39 g., b.p. 45-52°/0.05 mm.) and finally a third fraction (mixture C; 6.43 g., 52%) at 140-2°/0.05 mm.

Anal. Calc. for $C_{22}H_{52}Sn_2$: C, 48.23; H, 8.40. Found: C, 48.26; H, 8.44.

G.I.p.c. showed that fractions one and two were unreacted mixture A and tributyltin hydride. These were combined and photolyzed again in a pyrex tube for 30 hours at 65°. Distillation gave a small fraction (0.4 g.) at 35°/0.02 mm. and mixture C (1.1 g.) at 135°/0.02 mm.

Preparation of Nortricyclyl trimethyltin (Compound I). -

3-Bromonortricyclyne (14.4 g.) was added slowly to magnesium turnings (2.22 g.) in dry ether (100 ml.) with stirring. The resulting Grignard compound was refluxed for two hours. It was then cooled to 0° and a solution of trimethyltin chloride (16.6 g.) in 50 ml. dry ether was added to it in two hours. The mixture was again refluxed for two hours, cooled to 0° and then hydrolyzed by saturated ammonium chloride solution. The etherial layer was separated, washed with water, dried over magnesium sulphate and distilled. Nortricyclic trimethyltin (13.2 g., 62%) was obtained as a colorless liquid at 35°/0.02 mm.

Attempted Reaction between Nortricyclyl Trimethyltin and Trimethyltin Hydride. - A mixture of nortricyclic trimethyltin (4.5 g.) and trimethyltin hydride (5.0 g.) was photolyzed in a sealed pyrex tube for 18 hours at 65°. After removing unreacted trimethyltin hydride, the residual liquid was found to be unchanged nortricyclic trimethyltin contaminated with a little hexamethyltin.

Interaction between Norbornadiene and Tributyltin Hydride. -

A mixture of norbornadiene (1.8 g., 1 mole) and tributyltin hydride (5.8 g., 1 mole) was photolyzed in a pyrex ampoule for 18 hours at 65°. Distillation of the product yielded a mixture (D) of monoadducts (6.5 g., 85%) at 102°/0.02 mm.

Anal. Calc. for C₁₉H₃₆Sn: C, 59.58; H, 9.40. Found: C, 59.49; H, 9.37.

Interaction between Mixture (D) and Trimethyltin Hydride. - Trimethyltin hydride (3.8 g., 1.5 mole) was added to mixture (D) (5.8 g., 1 mole) in a pyrex tube. The photolysis was carried out for 30 hours at 65°. Distillation afforded four fractions having b.p. 115-125°/0.02 mm; 125-130°/0.02 mm; 130-135°/0.02 mm and 135°/0.02 mm. G.I.p.c. showed

that the last fraction (3.1 g., 37%) was a mixture (E) of the bisadducts whereas the first three fractions were mixtures of unreacted mixture D and the product.

Interaction between Mixture (B) and Trifluoroacetic Acid. -

Trifluoroacetic acid (2.5 g., 6 mole) was added to mixture (B) (1.42 g., 1 mole) in dry pentane (50 ml.). The mixture was stirred at room temperature for four days. Precipitation of a white solid started after 7-8 hours and gradually increased with slow evolution of methane. The white ppt. was filtered off and washed with more pentane and dried at 0.02 mm. The infrared spectrum shows that all methyl groups have not been cleared.

Preparation of 2(or 3)-TrimethylstannyI-5(or 6)-thiophenylbicycloheptane

It was prepared from the mixture (5.10g., 1 mole) and thiophenol (3.3g., 1.5 mole) by the same method as in the previous experiment and distilled at 137-39°/0.02 mm. (5.5g., 75%).

Found: C, 52.11; H, 6.55; S, 8.54; Sn, 31.72%. $C_{16}H_{24}SnS$

Requires: C, 52.33; H, 6.54; S, 8.72; Sn 32.36.

Preparation of 2(or 3)-TrimethylstannyI-5(or 6)trichloromethyl-6(or 5)-chlorobicycloheptane

Carbon tetrachloride (4.60g., 1.5 mole) was added to the mixture of trimethylstannylbicycloheptene (5.1g., 1 mole) in a pyrex tube which was sealed and photolysed for six hours. Distillation under reduced pressure afforded the addition compound as a colorless liquid (6.5g., 80%) b.p.: 113-14°/0.02 mm.

Found: C, 32.3; H, 4.40; Cl, 34.37; Sn, 27.98%. $C_{11}H_{18}SnCl_4$

Requires: C, 32.14; H, 4.38; Cl, 34.57; Sn, 28.89%

E. NITROGEN-CONTAINING ORGANOTINS

Preparation of 3-bromoquinoline. - In a three-necked flask, fitted with a condenser, a mechanical stirrer and a dropping funnel was heated, evacuated and filled with nitrogen gas. Redistilled quinoline, 39 g. (0.3 mole) and 320 ml. of anhydrous carbon tetrachloride were placed in the flask, 48 g. (0.3 mole) of Bromine was added slowly to the mixture. The mixture was heated for reflux about one hour thereafter, a solution of 23.7 g. (0.3 mole) of anhydrous pyridine in 20 ml. of carbon tetrachloride was added slowly to the refluxing mixture over a period of two hours. During the terminal 18 hours reflux period, the original orange suspension became tan-colored. Filtration of the cooled suspension, removal of solvent from the filtrate and fractional distillation afforded 36 g. (60% yield) of 3-bromoquinoline, b.p. 94°/2.25 mm.

Preparation of trialkyltin quinoline. - In a 3-necked round-bottomed flask, fitted with a condenser, a mechanical stirrer and a dropping funnel was evacuated and filled with nitrogen gas. n-Butyl-lithium (1.6 g. 0.025 mole) in hexane was placed in the flask together with 100 ml. of anhydrous ether. The flask was cooled by means of dry-ice-acetone bath to -50°. 3-Bromoquinoline (5.2 g. 0.025 mole) was introduced very quickly to the mixture. The color of the mixture became dark red. Color test for quinoline lithium was positive after fifteen minutes. Equivalent amount of trialkyltin chloride was added to the mixture; it turned to a yellow color after twenty minutes. The mixture was hydrolyzed with saturated ammonium chloride solution after several hours stirring. The ether layer was dried; after removal of ether, the liquid became viscous.

Preparation of 2-chloro-4-methyl quinoline. - In a 3-necked round-bottomed flask, fitted with a condenser, a mechanical stirrer and a dropping funnel was placed 29.4 g. (0.2 mole) of 2-hydroxy-4-methyl quinoline. About 60 ml. of phosphorous oxychloride was added slowly to the flask with cooling. After refluxing for twelve hours, the mixture was hydrolyzed with cold water. It was then extracted with convenient amounts of ether and dried over anhydrous magnesium sulfate. Removal of ether yielded 65% of corresponding 2-chloro-4-methyl quinoline, m.p. 53-54°.

Preparation of 2-triethyltin-4-methyl quinoline. - The same procedure as previously described for the preparation of 3-trialkyltin quinoline was employed.

Preparation of 3-(tributylstannyloxy) quinine. - Quinine (3.2 g., 0.01 mole) and bistributyltin oxide (3 g., 0.005 mole) in toluene (60 ml.) were heated under reflux for 1.5 hrs., with a Dean and Stark separator to remove water. The toluene was removed by pumping at a rotary pump, leaving an extremely viscous oil, the infrared spectrum of which showed no -OH band at 3120 cm^{-1} . On exposing the infrared plates to air for two minutes, the oil became a semi-solid, which the infrared spectrum showed to consist largely of quinine and bistributyltin carbonate.

Addition of acceptors to the alkoxide.

(a) Phenyl isocyanate. - To .01 mole of the tin alkoxide dissolved in carbon tetrachloride (10 ml.) was added phenyl isocyanate (1.19 g., .01 mole). The mixture was stirred rapidly for 30 minutes, heat being evolved on initial mixing. Volatile components were removed at the pump, leaving a viscous oil; the latter was readily hydrolyzed by

atmospheric moisture, and on ethanolysis, followed by treatment with pentane, gave a highly viscous oil containing no tributyltin compounds. This oil was sublimed in vacuo, yielding a white powder, melting slowly over the range 70-110°, ν_{max} 1730s (C=O) cm^{-1} .

(b) Chloral. - To .01 mole of the tin alkonide, dissolved in carbon tetrachloride (10 ml.) was added chloral (1.47 g., .01 mole). Immediately polychloral was formed, but on stirring for several hours dissolved. Volatile components were removed, leaving a readily hydrolyzed highly viscous oil. On methanolysis this yielded a white solid, m.p. 137-147°, the infrared spectrum of which showed no -OH bands.

Preparation of N¹-tributylstannylsulfanilamide. - Sulfanilamide (3.4 g., .02 mole) and bistributyltin oxide (5.96 g., .01 mole) in nylene (70 ml.) were heated under reflux for 2.5 hours with a Dean and Stark separator to remove water. The solvent was removed at a rotary pump, leaving a white crystalline solid. This was further purified by washing rapidly in air with dry pentane. An attempt to recrystallize a sample from toluene in air, taking no precautions to exclude atmospheric moisture, resulted in hydrolysis of the sample.

Preparation of Alkylpyridytins. - The method of preparation of all of these compounds is essentially the same; tributyl 3-pyridyltin will be quoted as an example.

To 3-bromopyridine (3.16 g., .02 mole) in ether (25 ml.) cooled to -40°, was added a solution of n-butyl lithium in hexane (13.4 ml. of 1.6 M). A brown precipitate was thrown down. Tributyltin chloride (6.5 g., .02 mole) was added, and the mixture stirred for two hours, during which time it was allowed to warm to room temperature and the brown color disappeared.

A saturated solution of ammonium chloride (40 ml.) was added; the ether layer separated and dried over magnesium sulfate. The ether was removed, leaving a pale orange oil, shown by G.L.C. to consist of two components, the minor one being tributyltin chloride. Distillation gave a pale orange oil, b.p. 106.5-108°/.075 mm; the G.L.C. of this indicated it to be 97% pure tributyl 3-pyridyltin.

Some of the other pyridyltins were obtained as brown oils; the brown color was removed by passing an ether solution through a short alumina column.

Table VI
ANALYTICAL DATA ON PYRIDYLTINS^a

	%C		%H		%N	
	calc.	found	calc.	found	calc.	found
tri-n-butyl-3-pyridyltin	55.4	55.3	8.4	8.3	3.8	3.4
di-n-butylbis-(3-pyridyl)tin	55.5	55.6	6.7	6.9	7.2	7.2
tri-n-propyl-3-pyridyltin	51.5	51.4	7.8	7.8	4.3	4.4
di-n-butylbis-(2-pyridyl)tin	55.5	55.7	6.7	7.0	7.2	7.0

^a All isolated as oils.

Preparation of Dimethyltin Dichloride - Bissalicylidenediaminoethane Adduct. - Dimethyltin dichloride was stirred and dissolved in benzene to which bissalicylidenediaminoethane in benzene was added. Yellow precipitates appeared immediately. They were filtered off and had m.p. of 149 to 153 C. Recrystallization from benzene-heptane mixture raised the m.p. to 153 to 154 C. The crystals were dried under reduced pressure at 80 C.

Found: C, 44.52; H, 4.59; N, 5.83; Cl, 14.70; Sn, 24.6

Calcd. for $C_{18}H_{22}N_2O_2Cl_2Sn$

C, 44.30; H, 4.55; N, 5.74; Cl, 14.53; Sn, 24.32

Diethyltin dichloride - Bis(salicylidenediaminoethane Adduct). -

Diethyltin dichloride (2.48 g., 0.01 mole) in 10 ml of benzene was added to bis(salicylidenediaminoethane) (2.68 g., 0.01 mole) in 30 ml of benzene with stirring. Yellow precipitates came out immediately. They were dissolved by adding 60 ml of benzene and 50 ml of n-heptane. The solution was kept to stand overnight to yield yellow crystals, m.p. 161.5 - 162.5 C.

Found: C, 46.77; H, 5.15; N, 5.42; Cl, 13.64; Sn, 22.9

Calcd. for $C_{20}H_{26}N_2O_2Cl_2Sn$

C, 46.55; H, 5.08; N, 5.43; Cl, 13.74; Sn, 23.00

Di-n-propyltin dichloride - Bis(salicylidenediaminoethane

Adduct. - Di-n-propyltin dichloride (2.76 g., 0.01 mole) in 10 ml of benzene was added to the ligand (2.68 g., 0.01 mole) in 30 ml of benzene with stirring. Yellow precipitates came out immediately which were recrystallized from 90 ml of benzene and 50 ml of n-heptane to yield yellow crystals, m.p. 109-110 C.

Found: C, 48.81; H, 5.62; N, 5.15; Cl, 13.29; Sn, 21.4

Calcd. for $C_{22}H_{30}N_2O_2Cl_2Sn$

C, 48.57; H, 5.56; N, 5.15; Cl, 13.03; Sn, 21.81

Ethyltin Trichloride - Bis(salicylidenediaminoethane Adduct). -

Ethyltin trichloride (2.54 g., 0.01 mole) in 10 ml of benzene was added to the ligand (2.68 g., 0.01 mole) in 30 ml of benzene with stirring. Yellow precipitates came out immediately. The solubility of this complex was so low that recrystallization was not tried. The precipitates

were filtered off and washed with n-pentane several times to give yellow powder, m.p. 191-3° C.

Found: C, 41.24; H, 4.09; N, 5.43; Cl, 20.21; Sn, 22.6

Calcd. for $C_{18}H_{21}N_2O_2Cl_3Sn$

C, 41.38; H, 4.05; N, 5.36; Cl, 20.36; Sn, 22.72

Preparation of Di-n-butyl(bisalicylenedimino)tin. -

Bu_2SnO (0.023 mole, 5.7 g.) and $BSDE2H$ (0.02 mole, 5.4 g.) were mixed in 100 ml of toluene and heated to reflux for five hours, filtered when hot and concentrated to give 9.7 g. of yellow precipitates, m.p. 100-200 C.

7.2 g. of these precipitates was passed through a column using neutral alumina and T.H.F. The solid left when the solvent was evaporated was recrystallized from benzene-heptane mixture to give 3.8 g. of yellow needle crystals, m.p. 80-200 C. The n.m.r. spectra showed fairly good intensity ratio of our kinds of protons. 3.8 g. of crystals were fractionally recrystallized several times and ended up with less than 1 g. of yellow needle crystals, m.p. 152-154 C.

Calcd. for $C_{24}H_{32}N_2O_2Sn$

C, 57.75; H, 6.48; N, 5.61; Sn, 23.77

DISTRIBUTION LIST

20 copies Defense documentation Center
Attn: DDCIR
Cameron Station
Alexandria, Virginia 22314

1 copy Commanding Officer
U. S. Army Combat Development Agency
Medical Service Agency
Brooke Army Medical Center
Fort Sam Houston, Texas 78234

4 Copies Commanding General
U. S. Army Medical Research and
Development Command
Office of the Surgeon General
Attn : MEDDM-SI
Washington, D. C. 20314

16 copies Director
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
Attn: Division of Medicinal Chemistry
Washington, D. C. 20012

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author) The Research Foundation of the State University of New York Albany, New York 12224		2a. REPORT SECURITY CLASSIFICATION none
2b. GROUP		
3. REPORT TITLE ORGANOTINS FOR ANTIMALARIAL SCREENING		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) Final report covering period 15 June 1966- 31 October 1968		
5. AUTHOR(S) (First name, middle initial, last name) Henry G. Kuivila		
6. REPORT DATE 5 January 1973	7a. TOTAL NO. OF PAGES 48 pages	7b. NO. OF REFS 18
8a. CONTRACT OR GRANT NO. DA-49-193-MD-3018	8b. ORIGINATOR'S REPORT NUMBER(S) Report no. 7	
9a. PROJECT NO.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)	
10. DISTRIBUTION STATEMENT Distribution of this document is unlimited. 20 copies Defense Documentation Center; 4 copies Commanding General, U. S. Army Medical Research & Development Command; 1 copy Commanding General, U. S. Army Combat Development Command, Medical Service Agency. 16 copies Walter Reed Army Medical	11. SUPPLEMENTARY NOTES Center, Medicinal Chemistry.	
12. SPONSORING MILITARY ACTIVITY U. S. Army Medical Research and Development Command		
13. ABSTRACT It was proposed to prepare for antimalarial screening organotins in four general categories: 1) preparation of a variety of relatively simple organotins for general screening; 2) introduction of organotin groups into quinine its derivatives; 3) introduction of organotin groups into 4-aminoquinoline; 4) introduction of organotin groups into sulfones which had shown some antimal- arial activity. During the course of the contract it was possible to carry on research on three of these categories. However, successful synthetic results were obtained only in the first of these. A total of forty three compounds was submitted for testing, and test results were returned on thirty six of these. These included: unsaturated fulfones; alkylallyltins; alkylallenyltins; alkylpyridines; bicycloheptyltins; and bis-salicylidenediaminocethane- alkyltin halide complexes. Some showed activity in mice, but were inactive or toxic in chicks; and vice versa. None was active in both, and many were toxic in one or both.		

DD FORM 1473

REPLACES DD FORM 1473, 1 JAN 64, WHICH IS
OBSOLETE FOR ARMY USE.

Security Classification

Security Classification

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT.	ROLE	WT.	ROLE	WT.
antimalarials						
organotins						
allyltins						
allenyltins						
pyridyltins						

Security Classification